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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,668	02/09/2001	Stephen D. Gillies	LEX-011	8264

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EXAMINER
SAUNDERS, DAVID A

ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 06/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/8/02

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-47 is/are pending in the application.
Of the above, claim(s) 20-23, 42, 44 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-19, 24-41, 43, 45-47 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☑ The drawing(s) filed on 2/9/01 is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☑ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

Claims 1-47 are pending.

Applicant's election of Group I (claims 1-19, 24-41, 43 and 45-47) in Paper No. 8, filed on 3/8/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application-by-application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The first page of the declaration states that the application was amended on 2/9/2001. No such amendment exists in the record.

The draftsman has approved the Figures filed on 2/9/01.

The drawings are objected to by the examiner because Figure 5 has no legend that indicates what the different plot characters are. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

It is noted that Figure 5 is described at specification page 30, with an indication of what the blacks diamonds and filled circles represent. There is no indication of what the open circles represent.

Any correction to Fig. 5 must not enter new matter not supported by the description of Fig. 5 in the specification.

Claim 25 is objected to under 37 CFR 1.75(c) as an improper multiple dependent claim because it depends from another multiple dependent claim.

Claims 1-19, 24-25, 36-37, 39-40, 43 and 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing by reciting a "junction point". From the various dictionary definitions of a "point" one would take "point" in the recited context to mean "a narrowly localized place having a precisely indicated position" or "a definite position on a scale" (residue position instantly). While claim 1 per se may appear definite, it becomes confusing when one reads in the limitation of claim 24 reciting "linker". Since the "linker" comprises multiple amino acid residues (e.g. 3 or 6) it cannot constitute a "point" or "definite position" in the sequence of amino acid residues. Where then is the "junction point" – at the N-terminal or at the C-terminal end of the linker? This raises the questions as to what the metes and bound of the invention may be. For example, consider a fusion protein, according to claim 1 without a linker, that has an altered residues in the C-terminal of the Ig-protein that is 8 amino acid residues from the junction point. Such a fusion protein is encompassed by the claim. Now add a 6-residue linker. If the junction point is defined as being at the N-terminus of the linker, then the Fusion protein is still encompassed. On the other hand, if the junction point is defined as being at the C-terminus of the linker, then the fusion protein is no longer encompassed since the altered residue is now 14 residues way from the junction point.

Claims 9 and 10 recite various amino acid residues that can be altered in IgG1 or IgG3. It is not clear what species of IgG1 or IgG3 is recited – rabbit, mouse, human? It is also not clear what the numbering system is – that of Kabat?

In claim 18 "said colony stimulating factor" lacks antecent basis.

In claim 12 "substantially reduced" is unclear – "reduced" in comparison to what?

In claim 36 "polypeptide is mutated to be an amino acid" is confusing.

In claims 39 and 40 "spacer or linker peptide" is unclear. Are these the same (redundant recitations) or different both? Is peptide modified by "spacer" and "linker" or only by "linker"? If "spacer" is not necessarily a "peptide", then clam 39 is inconsistent with base claim 26 because the term "fusion protein" refers to a construct in which the fused portions are joined by peptide bonds.

Claim 43 depends from non-elected claim 42.

The term "near" in claims 45-47 is a relative term, which renders the claim indefinite. The term "near" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "near" is indefinite because applicant apparently contemplates embodiments in which the mutation in the "junction region" (claim 26) could be at least 100 amino acid residues removed from the junction (claims 30 and 32).

Given such a wide breadth of what could be encompassed by "near", it is not clear whether "near" in claim 45 is to be read as "within 10 amino acids from said junction point" when claim 45 is read as depending from claim 1.

Claims 1-19, 24-41, 43 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has not adequately described the genus of fusion polypeptides that are claimed.

Applicant has not provided sufficient examples within the genus that would permit one to envision the structural nature of altered fusion proteins that constitute the whole genus.

First one has no grasp as to what a "junction point" is (see 112, second rejection supra) when there is a linker present; thus one does not then know what alterations are within 10 amino acids and which are more than 10 amino acids any from the "junction point".

Also one has no grasp of what a "junction region" is, since applicant considers that mutations in the "junction region" could be 100 or more amino acid residues away from the joining point of the first and second polypeptides constituting the fusion protein.

Thus one cannot adequately envision where the "alteration" or "mutation" is to be made in the fusion protein of either claim 1 or claim 26.

Second, even if one knew where to make the "alteration" or "mutation" in the sequence, there is inadequate direction as to what kinds of alterations/ mutations fall within the full extent of the genus.

where purge 6

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 26-27, 30, 34-35 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Gillies et al (WO 99/43713).

Gillies et al teaches fusion proteins consisting of an Ig-polypeptide and a non-Ig-polypeptide that have an enhanced circulating half-life. In cases in which the Ig-protein is IgG1 or IgG3, various particular residues can be deleted, mutated, or inserted. See page 3, lines 4-13.

Rejection is properly stated because the term "junction region" in claim 26 is properly interpreted as broad enough to encompass fusion proteins having mutations introduced at a position at least 100 residues removed from the junction point between the first and second polypeptide.

Claim 30 is properly included in the rejection because a mutation at the Pro 331 or Pro 378 positions, taught by Gillies et al, would be within 100 residues of the C-terminus of the Ig-polypeptide (assuming 440 resides for an Ig-heavy chain).

Claims 26-27, 30, 34-35 and 38 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/256,156 (refilled as a CPA) which has a common assignee and inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application. Copending application 09/256,156 has a disclosure equivalent to that of WO 99/43713 cited supra. The provisional 102(e) rejection is made on the same basis as the 102 (a) rejection supra.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-27, 30, 34-35 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09/256,156. Although the conflicting claims are not identical, they are not patentably distinct from each other because The instantly rejected claims, are consistent with the invention of the listed copending claims. The instant and copending claims therefore, encompass common subject matter. A disclaimer is required in order to assure further common ownership of patents with common subject matter in the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 26-27, 34-35, 38 and 45-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Gillies et al (Cancer Res 59, 2159, 1999).

Gillies et al disclose essentially the same fusion proteins as in WO 99/43713 cited supra. More specifically they show an increased half - life fro an IgG1 fusion protein, which has mutations at positions 233-236. See page 2160, col. 1. Applicant's claim language reciting "junction region" (claim 26) is so vague that anticipation is properly stated over the disclosed fusion protein.

Dependent claims 45-47 are also properly rejected since "near said junction" is sufficiently vague (112, second rejection supra) to warrant anticipation. The substitutions disclosed by Gillies et al include introduced val and ala residues, which are hydrophobic and non-polar, respectively.

Claims 26, 35, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Strom et al (WO 96/18412) in light of Gillies et al (WO 99/43713).

Strom et al show a fusion protein with a cytokine at the N-terminal and an immunoglolulin hindge region and Fc at the C-terminal. In the CH2 dormain thereof, mutations are introduced as shown in Fig 1 and as discussed at page 10, lines 27 + and page 12, line 30 – page 13, line 5. The mutation at position 235 serves to reduce the affinity of the fusion protein for the high affinity Fc receptor (page 10). Gillies et al are relied upon for teaching that such a mutation serves to extend the circulating half-life of a fusion protein. Thus external evidence is cited to show that the mutation at position 235 inherently provided the property now claimed.

The mutation at position 235 is reasonably considered to be within the "junction region" of the fusion protein, since instant claims 30 and 32 would permit a mutation at a point 100 or more resides from the junction point.

Claims 1-2, 5-8, 11-13, 25-26, 35, 43 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Browne et al (WO 97/00319).

Browne et al disclose a fusion protein constituted of a leptin at the N-terminal, an Ig hindge region, and an Ig Fc at the C-terminal. Browne et al disclose IgG4 constructs wherein residue 10 of the hindge region (241 of kabat) is altered from ser to pro. This

increases the serum half-life. See page 2, line 19 – page 3, line 11; page 13, lines 17-23. This mutation is within 10 residues from the junction point.Hence claims 1 and 26 are properly anticipated. The pro residue is more hydrophobic than the ser residue; hence claims 2 and 45 are anticipated.

Regarding dependent claims with limitations not addressed supra, note that Browne et al's construct has the mature form of the leptin polypeptide. Note page 1, lines 12-17; and page 13, lines 36-40.

With respect to claim 11, the fusion protein of Browne et al is deemed to inherently have binding affinity for the Fc Rp receptor, since Browne et al (Example 2) disclose no mutations at positions 253, 310, or 435 which applicant has disclosed (instant page 4) as critical for such binding.

Claim 12 is included because IgG4 has "substantially reduced" binding affinity for the recited Fc receptors, in comparison to other IgG isotypes (IgG1-3).

Claims 1-2, 5, 7-8, 11-14, 26-33, 35, 39-41, 43 and 45-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Chang et al (5,908,626).

Chang et al disclose fusion proteins of IFN beta and Ig Fc at the N-and C-terminals, respectively. These are joined at a "junction region" by a linker comprised of gly and ser. It is deemed that this linker inherently increased the circulatory half-life of the fusion protein, since the composition of gly and ser is consistent with applicant's description of a linker at pages 9-10 and in Examples 9-11. What is shown by Chang et al is thus consistent with instant claims 1-2, 7, 24, 26, 35, 39-40, 43 and 45-46.

In further support of the examiner's position that the fusion protein of Chang et al would have a longer circulating half-life, it is noted that Chang et al teach that the linker reduces immunogenicity of the fusion protein (e.g. col, 2, lines 10-20 and col. 3, lines 5-16). Thus the presence of this linker reduces the chance of inducing the production of antibodies that would otherwise clear the fusion protein from the serum.

Claim 5 is included since TNF beta is a secreted protein.

Regarding claim 8, Chang et al teach an IgG4 constant region.

Claims 11 and 41, are considered anticipated since Chang et al disclose no mutations at positions 253, 310 or 435 involved in FcRp binding or at positions involved other FcR binding.

Regarding claims 27-33, these are included because an added linker can be properly considered as involving insertions at the C-terminal of one member and at the N-terminal of the other member.

Regarding claims 13-13, TNF beta clearly falls within the scope of these claims.

Claim 12 is included since IgG4 has "substantially reduced" binding affinity for the recited receptors, compared to IgG1-3.

Claims 1, 5-8, 11-16, 26-33, 35, 39-41, 43 and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang et al (5,723,125).

Chang et al ('125) disclose essentially the same invention as that of Chang et al ('626) cited supra, except that the non-Ig polypeptide at the N-terminal is TNF alpha. The rejection is based on the rational stated supra, that the linker would inherently provide for an increased half-life of the fusion protein.

Claims 15-16 are included in the rejection, since Chang et al exemplify TNF alpha, and teach the same linker can be used in creating IL-2-Fc fusion proteins (col. 2, lines 60-67).

Claims 5-6 are included in light of the disclosure at col. 5, lines 21-35, teaching that mammalian cells can express the fusion protein with a native N-terminal.

Claims 1-2, 5-8, 11-14, 24, 26-33, 35, 39-41, 43, 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Gerrmann et al (6,100,387).

Gerrmann et al disclose fusion proteins of a chemokine and Fc portion of IgG, which are at the N-and C-terminals respectively. These are joined by a gly-ser linker (e.g. col. 20, lines 14-29 and col. 15, lines 6-22). Following the rational applied super to Chang et al, it is considered that this linker inherently imparts an increased half-life to the fusion protein. Thus claims 1-2, 7, 24, 26-33, 35 and 39-40, 43, and 45-46 are anticipated.

Claims 5 and 13-14 are included since chermokines are secreted proteins, and include IL-8. See col. 2, lines 18-50.

Claim 6 is included, since Herrmann et al teach provision of the mature form of chemokines (col. 9, lines 47-58).

Claim 8 is rejected since Herrmann et al exemplify the Fc region of IgG4 (Example 1).

Claims 11 and 41 are included because the inserted linker does not affect region that bind with FcRp or other Fc receptors.

Claim 12 is included because IgG4 has "substantially reduced" binding affinity for the recited receptors in comparison to other IgG isotypes.

Claims 13-18 are rejected based on the teachings at col. 5, lines 11+.

Claims 1-3, 5-19, 24, 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilles et al (WO 99/43713) in view of Chang et al ('626 or '125).

Gilles et al have been cited further supra. In this obviousness rejection it will be considered that the mutations shown by Gillies et al were introduced for the purpose of affecting changes in the binding of the fusion protein with various Fc receptors (in accord with instant claims 9-12) and that such mutations/ alterations are not located in the junction point/region.

Chang et al have been cited further supra for teaching that insertion of a gly-ser linker between the members of a fusion protein provides the advantage of reducing immunogenicity of the fusion protein. It thus would have been obvious to provide such linkers in the fusion proteins of Chang et al. In so doing, it is the Office's position that an increase in half-life would inherently result . Thus claims 1, 24, 26, 39-40, 43 and 45-46 would have been obvious.

The limitation of dependent claims 2 and 27-33 and 41 has been argued supra to be inherent upon insertion of the linker.

The limitations of claims 3, 5-19 and 34 are consistent with the teachings of Gillies et al.

All of the above 102/103 rejections based on the assertion that insertion of a gly-ser linker would inherently increase the half-life are reasonably based on the fact that

such a linker has the essential nature of those contemplated and exemplified by applicant. In the absence of laboratory facilities at the USPTO to compare half-life of fusion proteins with and without such linkers, the burden lies upon applicant to show a comparison.Ex parte Gray 10 USPQ 2d 1922.

Applicant should also address the above 112/102/103 rejections by presenting claims that more definitely describe the position of the junction point alteration/mutation, as well as the nature of the alterations/mutations.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Saunders whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday to Thursday from 8 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

Saunders/dl

June 17, 2002